FDA Regulation of In Vitro Diagnostic Tests

FDA Public Meeting on Oversight of Laboratory Developed Tests
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Agenda

- General introduction to FDA and IVD regulation
- How does FDA regulate IVDs?
  - Device Classification
  - Premarket Review
  - Postmarket Requirements
- Information and Resources
Legal Basis of Regulation

• Authority to regulate medical devices
  • Public Health Services Act
  • Federal Food Drug and Cosmetic Act (FFDCA) of 1938
  • Medical Device Amendments 1976

• Other legislation
  • FDA Modernization acts of 1997, 2002 and 2007
FDA Regulation of Medical Devices

• 1976 Device Amendments modified the Act to provide for the regulation of Medical Devices

• Medical Devices: “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or similar related article. . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals” (FFDCA 201(h))
Definition of IVDs

• IVDs are a subset of medical devices which are “reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae” (21 CFR 809.3)
Risk-Based Classification of IVDs: Intended Use

• The classification of an IVD is risk-based, and determined based upon the intended use of the device

• Intended Use:
  – General description of the disease or condition that the device will diagnose, treat, prevent, cure or mitigate
  – Defines the patient population
  – Defines specific type of specimen

• A single IVD can have multiple intended uses
Intended Use Statement (2)

- Example: Pregnancy Test

“The X urine test is an immunoassay designed for the qualitative determination of human chorionic gonadotropin (hCG) in urine for the early detection of pregnancy. It is intended for professional use.”
Risk-Based Classification of IVDs

- The risk of an IVD is based on the consequences of a false result
- 3 Classification levels
  - Class I: common, low risk devices
  - Class II: more complex, moderate risk
  - Class III: most complex, high risk and novel intended uses
IVDs: Classification Breakdown

Percentage of IVD Devices by Product Class

- Class I: 50%
- Class II: 42%
- Class III: 8%
Class I IVDs

• Represent common, low-risk devices

Examples:
  • lactic acid
  • erythrocyte sedimentation rate test
  • differential culture media

• Most exempt from premarket submission
• General Controls are required
General Controls

- Applicable to medical devices, regardless of class
- Registration and listing
  - Manufacturers must register their manufacturing facilities, and list the devices they manufacture
- Good Manufacturing Practices (GMP)
  - Devices must be manufactured in a controlled manner as per 21 CFR Part 820 (Quality System Regulation)
- Reporting of Adverse Events and Recalls
- Device Labeling Provisions
  - Prohibition against misbranding, adulteration, false or misleading claims, sales of banned devices
- Maintenance of Records and Provision of reports to FDA
Class II IVDs

- Moderate risk devices, tend to be more complex
- Examples:
  - factor deficiency test
  - antimicrobial susceptibility test systems
  - thyroid stimulating hormone test system
- Premarket Notification [510(k)]
- Special Controls
- General Controls
Premarket Notification: 510(k)

- 510(k) submission required of most class II devices
- Submission has 90 day review clock
- FDA clearance based on “substantial equivalence” to legally marketed device (predicate device)
- What substantial equivalence to predicate device means:
  - Similar intended use
  - Similar performance characteristics
- What substantial equivalence does NOT mean
  - Identical technology
- Submissions may require clinical data
- Summary of FDA’s review and basis for decision is posted on the FDA website
Special Controls

• **What they are:**
  – Special requirements for devices when the general controls alone are insufficient
  – May include:
    • special labeling requirements
    • mandatory performance standards
    • postmarket surveillance

• **Special controls are described through guidance documents which are posted on FDA’s website**
Class III IVDs

• Represent highest risk, most complex devices, novel intended uses
  Examples:
  • Hepatitis B and C, HPV tests
  • Total PSA for prostate cancer screening
  • Continuous Glucose Monitoring Devices
• Premarket Application [PMA]
• Submissions often include clinical data
Premarket Application (PMA)

- 180 day review clock
- Demonstration of safety and effectiveness
- Does not use predicates
- Submissions often include clinical data
- Pre-approval inspection performed
- FDA may seek may require advisory panel decision prior to approval
- Summary of Safety and Effectiveness Data (SSED) posted publicly on web
De novo

- Used for devices:
  - that do not have a legally marketed predicate
  - are not high risk
  - the risks that do exist can be mitigated through Special Controls
- Reviewed for safety and effectiveness
- Used as a mechanism for down classification of devices
  - Special controls implemented
  - Classification published
  - De novo device becomes predicate for future devices of same type with same intended use
- Has been an important tool for novel IVDs
Investigational Status Devices

- Most IVD investigations are exempt
  - If test does not introduce energy into a subject
  - If test results not returned to patient/physician
  - If no invasive measures needed to get sample or samples has been obtained from another procedure

- Investigational Device Exemption (IDE)
  - Required for non-exempt devices
  - Submission required for devices for which safety and effectiveness data is being gathered
  - 30-day review clock
  - Must be labeled for investigational use
  - Informed consent for samples
  - IRB approval of study
Premarket Review

All IVDs must establish adequate:

Analytical Validity
  • How accurately does the test measure the analyte?
  • How reliably?

Clinical performance
  • How reliably does the test measure the clinical condition?

Labeling (21 CFR 809.10)
  • Adequate instructions for use
  • Intended use, directions for use, warnings, limitations, interpretation of results, performance summary
Analytical Performance

- FDA recommends use of CLSI evaluation protocols to evaluate device performance

- Assess:
  - Repeatability/Reproducibility
  - Accuracy
    - “Truth” – may be a reference method, clinical endpoint, predicate device, etc…
  - Limit of Detection/Limit of Quantitation
  - Linearity
  - Potential Interferences/ Cross-Reactivity
  - Cross-contamination / Carry-over
  - Matrix effects
  - etc…
Clinical Performance

• Clinical Validity
  – Device must have a clinical indication
  – Device should add value to clinical management

• Clinical validity claims may be based on:
  • Existing clinical data (i.e. no new clinical data needed)
    • E.g. Sodium
  • New clinical trial data
  • Review of information in the literature
  • Current clinical knowledge
Clinical Performance

• Retrospective studies OK? Yes – IF:
  • the study supports the intended use of the test
  • samples were collected and stored appropriately in a manner that reflects current practice
  • no sampling bias

• Literature to support device
  • All published studies should be analyzed for their applicability to the device claims
Clinical Performance

• If a new clinical study is needed. . .
  – Study should clearly define samples/populations
    • Should represent Intended Use population
    • Prospectively collected (ideal)
    • Clearly defined inclusion/ exclusion criteria
    • Sample size/trial design statistically appropriate
  – Review of new clinical studies
    • Team of experts included in review e.g. statisticians, physicians
    • Use clinical practice and society guidelines in decision-making process
    • Often include input from outside experts, advisory panels as needed
Software/Instruments

- FDA regulates all software/instrumentation used in diagnostic test systems
- Total system validation
- Database integrity
- Cyber-security
- FDA has guidance on how to validate, present data for software:
  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm
Quality System Regulation (QS Reg)

• As per 21 CFR Part 820
  • Requires that manufacturers have an appropriate quality system and policies in place for their manufacturing operation
  • Regulation designed to be flexible for both large and small manufacturers
  • Appropriate trained personnel and facilities
  • Controlled
    • device design
    • purchasing, installation, and distribution
    • manufacture, packaging, labeling, storage, etc
  • Correction and prevention system
  • Complaint handling
  • Documentation
Medical Device Reports (MDRs)

• Reports to FDA by user facility/manufacturer when a device:
  • Caused or contributed, or may have caused or may have contributed to a death
  • Caused or contributed, or may have caused or may have contributed to a serious injury
  • Malfunctioned or failed to meet specifications (manufacturer only)
    • Recurrence could result in death or serious injury
• Required timeframe for reporting
  • 5-30 days, depending on severity
  • Follow-ups when needed
• FDA assesses reports and decides if action is needed
Recalls

- Method of removing or correcting products that are in violation of laws
- Products present a risk of injury or gross deception or are otherwise defective
- Usually voluntary by manufacturer, but must be reported to FDA
- FDA
  - Conducts health hazard evaluation (HHE)
  - Classifies recall
  - Posts recall information on website
  - Ensures manufacturer completes recall
FDA Enforcement

- Carries out inspections of manufacturing facilities
- Acts on findings and allegations of violative activities
PreIDE Meetings

- Can be requested to discuss any future submission (not just IDEs)
- Informal review of sponsors’ proposed intended use, IVD validation plans, etc.
  - Flexible process
  - Not binding on FDA or sponsor
  - Can help sponsors refine intended use, and study designs
  - Good option for new sponsors, new tests
  - Can be a single interaction or multiple cycles
FDA Outreach

- 510(k) Workshop
  - OIVD participates in this each year to foster communication between the professional, manufacturing and regulatory communities
  - Provides education on submission requirements and strategies
  - Sessions led by FDA personnel who review 510(k) submissions
- FDA participation in workshops and conferences put on by device and medical societies
- FDA is willing to hold additional education and outreach workshops as needed
Small Manufacturers Assistance

- Division of Small Manufacturers, International and Consumer Assistance (DSMICA)
  - Provide assistance and guidance on pre- and post-market issues
  - Contact information:
    - Email: dsmica@fda.hhs.gov
    - Phone: 1-800-628-2041
Information on Cleared/Approved IVDs

• OIVD Review Decision Summary
  – Standard template with review data for 510(k)s
• 510(k) database
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
• PMA Safety and Effectiveness Summary
  • http://www.fda.gov/cdrh/pmapage.html
• For de novo 510(k)s, Special Controls Guidance Documents available
  • Describes 510(k) submission requirements for devices of same type with same/similar intended use
  • http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm
Accessing Review Decision Summaries

510(k) database:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
Accessing Review Decision Summaries

### 510(k) Premarket Notification Database

| Device Classification Name | Classifier, Prognostic, Recurrence Risk Assessment, Rna Gene Expression, Breast Cancer |
| 510(K) Number              | K062894                                                                 |
| Device Name                | MAMMAPRINT                                                                |
| Applicant                  | AGENDIA BV                                                                 |
| Louwesweg 6                | Amsterdam, NL 1088 EC                                                     |
| Contact                    | Guido Brink                                                                |
| Regulation Number          | 666.6040                                                                  |
| Classification Product Code| NYI                                                                      |
| Date Received              | 09/11/2006                                                                |
| Decision Date              | 02/06/2007                                                                |
| Decision                   | Cleared For Marketing Automatic Class Iii Designation (AN)                |
| Classification Advisory Committee | Immunology                                                               |
| Review Advisory Committee  | Immunology                                                                |
| FOI ITEM                   | LETTER                                                                    |
| FDA Review Type            | Decision Summary                                                          |
| Reviewed By Third          | Cleared For Marketing Automatic Class III Designation                     |
Review Decision Summaries

Decision Summary contains the information used to support clearance:

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k062694

B. Purpose for Submission:
New device

C. Measurand:
70 gene expression profile

D. Type of Test:
Expression microarray
Test service performed in a single laboratory in Agenda’s Amsterdam facility.

E. Applicant:
Agendia BV

F. Proprietary and Established Names:
MammaPrint®

G. Regulatory Information:
1. Regulation section:
   21 CFR 866.6040 Gene expression profiling test system for breast cancer prognosis
2. Classification:
Accessing Summary of Safety and Effectiveness

PMA Database:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm
Accessing Summary of Safety and Effectiveness

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<tr>
<th>Trade Name</th>
<th>CONTINUOUS GLUCOSE MONITORING SYSTEM</th>
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<tbody>
<tr>
<td>Classification Name</td>
<td>Sensor, Glucose, Invasive</td>
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<tr>
<td>Generic Name</td>
<td>Continuous Subcutaneous Glucose Monitoring System</td>
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<tr>
<td>Applicant</td>
<td>MEDTRONIC MINIMED</td>
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<td>PMA Number</td>
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<td>Date Received</td>
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<td>Decision Date</td>
<td>06/15/1999</td>
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<td>Product Code</td>
<td>MDS [ Registered Establishments With MDS ]</td>
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<td>Docket Number</td>
<td>99M-2169</td>
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<td>Notice Date</td>
<td>07/14/1999</td>
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<td>Advisory Committee</td>
<td>Clinical Chemistry</td>
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<td>Expedited Review Granted?</td>
<td>Yes</td>
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<td>Information About:</td>
<td>Labeling, Approval Order, Summary Of Safety And Effectiveness</td>
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<td>Approval Order Statement</td>
<td>The device is intended to continuously record interstitial glucose levels in persons with diabetes mellitus. This information is intended to supplement, not replace blood glucose information obtained using standard home glucose monitoring devices. The information collected by the device may be downloaded and displayed on a computer.</td>
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</table>
Summary of Safety and Effectiveness

- General information
- Indications for Use
- Device Description
- Contraindications, Warnings, and Precautions
- Alternative Practices and Procedures
- Marketing History
- Potential Adverse Effects of the Device on Health
- Summary of Preclinical Studies
- Summary of Clinical Studies
- Conclusions Drawn from the Studies
- Panel Recommendations
- CDRH Decision
- Approval Specifications
Resources: Guidance Documents

• Provides the agency’s current thinking on a topic
• Initially issued in draft form, allow for public comment
• Examples of guidance documents:
  • In Vitro Diagnostic Device (IVD) Studies – Frequently Asked Questions
  • Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests
  • Guidance for the Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable
On-Line Resources: OIVD Webpage

• Access information relevant to IVDs
  • Regulations
  • Guidances
  • CLIA categorizations
  • Standards
  • Lab and user information

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm
On-Line Resources: CDRH Device Advice

• Website with information on medical devices
  • Guidance
  • Regulations
  • Databases
• Good place to look for explanations of how to make submissions, pre- and post-market requirements
• http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm
Thank you!